P2-006 **BSTB: Cancer Genetics Posters, Tue, Sept 4**

Homeobox gene HOP has a potential tumor suppressive activity in human lung cancer

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The homeobox containing gene LAGY (Lung Cancer Associated Gene Y Genbank accession Nr. AF454763), also named Hop (Homeodomain only protein), was identified in the developing heart and lung where it functions downstream of Nkx2.5 and Nkx2.1 to modulate cardiac and lung gene expression. Previously, we found that LAGY was downregulated in lung cancer cell lines and primary lung tumors and the downregulation was linked to higher tumor grading. In this study, we constructed an expression vector containing the full-length cDNA of LAGY and transfected it into a lung cancer cell line H2170. Stable transfection led to an increased expression of LAGY which was confirmed by Northern blot and Western blot analysis. LAGY positive transfectants remarkably reduced the growth rate as well as the ability of anchorage-independent growth in soft agar, and moreover, suppressed the tumor formation in immune-deficient nude mice compared to mock transfectant and parental cells. Transient transfection of Nkx2.1 into H2170 resulted in the overexpression of LAGY, and correspondingly, siRNA silencing of Nkx2.1 reduced the expression of LAGY in a lung cancer cell line H2228, the only lung cancer cell line expressing LAGY we found so far. Treatment with a differentiation modulating agent 5-bromodeoxyuridine (BrdU) led to restoration of LAGY expression in a small cell lung cancer cell line H526B. However, knockdown of LAGY expression in H526B by RNA interference (siRNA) neither caused any decreased expression in lung epithelial differentiation markers nor any changes in cell morphology, implicating that LAGY might not act as a differentiation trigger in lung cancer. In 29 paired primary lung tumors, loss of heterozygosity (LOH) analysis was performed by using three microsatellite markers D4S189, D4S231 and D4S392 around the region of chromosome 4q12 where LAGY locates. LOH was only found in 4 out of 23 cases (17.4 %), indicating that allelic loss is a rare genetic event not responsible for the downregulation of LGAY in lung cancer. Taken together, our data suggest that LAGY is a potential tumor suppressor involved in lung cancer differentiation, and possibly functions downstream of Nkx2.1.

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MRP1 and MRP3 protein and gene expression in non small cell carcinomas

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Background: Non-small cell lung carcinomas (NSCLC) are bronchogenic carcinomas characterized by their intrinsic resistance to chemotherapy and mechanisms of this clinical resistance are poorly known. The Multidrug Resistance Protein (MRP) family belong to the ATP binding cassette super family of transport proteins, which play a physiological role in defence against toxic compounds including carcinogens. Some MRPs have been shown to confer resistance to anticancer agents in various in vitro models.

Methods: In order to investigate the possible role of MRP1 and -3 in clinical drug resistance, protein and gene expression was analysed using, respectively, immunohistochemistry and RT-PCR (Light-cycler, Roche®) on tumoral tissue sample from patient who underwent surgery for localised NSCLC.

Results: 13 tumorals frozen samples were used, 8 were adenocarcinomas and 5 were squamous carcinomas. Regarding protein expression for MRP1 and -3, 10 samples were considering negative for MRP1 and 8 negative for MRP3, proteins expression was independent in each sample and according to histological sub-group. Regarding gene expression, all samples have positive expression for each gene; relative quantities for each gene were variable in each sample. No pattern of expression was found according to sample or histological sub group.

Relation between protein and gene expression was then analyzed. No relation was found for MRP1, all samples had positive gene expression and only 3 samples had a positive staining for MRP1. Analysis for MRP3, showed that a relation between protein and gene expression could exist. Positive staining for MRP3 were found in samples were gene expression were higher.

Conclusions: Gene and protein expression in tumoral non small cell lung cancer sample is not found for MRP1 and seems to be positive for MRP3, depending on a gene expression threshold. More samples need to be analyzed to confirm those results and survey for patient who underwent adjuvant chemotherapy is already studied.

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Influence of common glutathion-S-transferase and DNA repair variant alleles on p53 function: relation to lung cancer risk and progression

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Recent evidence suggest that polymorphism such as genes as GST M1 and T1, p53 and XRCC1, playing a critical role in neutralization of chemical carcinogens, cell-cycle arrest, DNA repair and apoptosis may provide additional risk for lung cancer. In fact, many studies have evaluated the relationships between polymorphism of the glutathion-S-transferase or DNA repair genes with the p53 protein function, but the results are equivocal.

Background: Bronchial epithelium is exposed to risk of damage by polycyclic aromatic hydrocarbons from a tobacco smoke or endogenous metabolic agents which can play a role of pro-carcinogens. Presents of the "null" genotypes of glutathion-S-transferase genes leads to a total loss of enzymatic activity, high level of activated carcinogens and DNA- adducts formation: benzo(a)pyrene diol epoxide-DNA-adducts may potentiate the mutation of p53 gene, involving in cell cycle arrest to allow repair DNA damage. p53 and XRCC1 genes has been identified as necessary components of the base excision repair for removing of spontaneous mutations in the cells. Numerous SNPs are located in exons or promoter regions of XRCC1 gene may alter the efficiency of the repair process.

Methods: Polymorphism of the GSTT1, GSTM1, p53 and XRCC1 genes was evaluated in 170 lung cancer patients and 200 healthy donors. GSTM1 and GSTT1 genotypes was determined by a multiplex PCR.